REMARKS

The claims of the present application have been amended to more particularly define the nature of the invention disclosed therein. In particular, Claim 18 has been amended to recite a novel composition suitable for the intracellular delivery of an exogenous compound. Specifically, Claim 18 is directed to a composition comprising a cationic cytofectin as described in Formula I in combination with an exogenous compound for intracellular delivery, said compound being selected from the group consisting of nucleic acids, peptides, peptide derivatives, proteins, protein derivatives, steroids, hormones, carbohydrates, and pharmaceutical compounds, and, optionally, the composition may include a neutral lipid. Support for the amendment to Claim 18 may be found throughout the specification, in particular, page 9 (compositions), page 7 (exogenous compounds) and page 5 (neutral lipids), as well as Example 4 beginning on page 14 and Example 5 beginning on page 21 of the specification.

Dependent Claims 19-32 have been amended to refer to the composition of Claim 18. New Claims 33-46, also dependent from Claim 18, have been added to recite particular embodiments of the novel composition disclosed throughout the specification.

Support for new Claim 33 may be found in the specification on page 5; support for new Claims 34-39 and 42 may be found in the specification on page 6; support for new Claims 40, 41, and 44 may be found in the specification on page 7; support for new Claims 45 and 46 may be found in the specification on page 8.

No new matter is added by the amendments to Claims 18-32 or the addition of new Claims 33-46. Entry of the amendments and allowance of Claims 18-46 are respectfully requested.

I. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20 and 23-27 under 35 U.S.C. §102(b) as anticipated by Milieva et al., *J. Appl. Toxicol.*, 15: 219-222 (1995). According to the Examiner,

> "Milieva discloses (abstract) the use of N,N,N'N'-tetramethyl-N,N'-di(8-15-dicloropentadeca-5,10-dien)ethylenediamine methylsulphate. Thus, k=1, n=2, i.e., B=ethyl, R1, R3, R4, and R6 are each methyl, and R2 and R5 are each pentadecadienyl." (See, Office Action, page 3.)

Milieva et al. report on the biphasic effect of a known fungicidal quaternary ammonium salt (QAS), on the mechanical and electrical activity of smooth-muscle samples from rat and guinea pig, i.e., depolarization followed by an increase in spontaneous contractile activity (phase 1) and

depolarization followed by inhibition of rhythmic activity (phase 2). (See, for example, page 221, left column.)

There is no disclosure in Milieva et al. concerning use of the QAS compound disclosed therein for transfection and no disclosure or suggestion for use of a QAS compound in a composition that includes an exogenous compound, e.g., DNA, protein, etc., whereby the QAS facilitates the intracellular delivery, i.e., transfection, of the exogenous compound.

Reconsideration and allowance of Claims 18-20 and 23-27 are respectfully requested.

II. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20, 23-25, and 27 under 35 U.S.C. §102(b) as anticipated by Sykora et al., *Folia Microbiol.*, 36(3): 240-245 (1991). According to the Examiner,

> "Sykora discloses (abstract) the use of N,N'-bis(decyldimethyl)-1,6-hexanediammonium dibromide. Thus, k=1, n=6, i.e. B=hexyl, R1, R3, R4, and R6 are each methyl, R2 and R5 are each decyl, and A is bromide." (See, Office Action, page 3.)

The Sykora et al. reference is directed to the analysis of the bactericidal, i.e., plasmid-curing (removal) effect of N,N'-bis (decyldimethyl)-1,6-hexanediammonium dibromide (BDHD) on *E. coli* and *S.typhimurium*.

Sykora et al. report on attempts to cure, i.e., eliminate, six different plasmids from *E. coli* (F'lac, R144, RP4, R6K, R16, and pKM 101) and one plasmid, pKM 101, from *Salmonella typhimurium*, by treatment of the cells with BDHD. According to Sykora et al., bacteria were grown in an overnight culture with the appropriate antibiotic, collected, incubated with fresh antibiotic-free LB plus varying concentrations of BDHD, and plated on agar plus antibiotic to select for colonies with plasmids. The percent of bacterial cells cured of plasmid, i.e., eliminated from the cell, was determined from the proportion of plasmid-less colonies.

However, there is no teaching or disclosure in Sykora et al. concerning the use of BDHD or any cationic cytofectin compositions for transfection, i.e., insertion of a foreign compound, e.g., plasmid DNA, into a cell and no disclosure or suggestion for use of BDHD in a composition that includes an exogenous compound, e.g., DNA, protein, whereby the BDHD is capable of intracellular delivery, i.e., transfection of the exogenous compound. Sykora et al. disclose contacting a bacterial cell with a quaternary ammonium salt *only*, i.e., not as a component of a composition, to remove a native or inserted DNA sequence from the bacterial cell. In fact, Applicants assert that one skilled in the art, after reviewing this reference, could only conclude

that the disclosure of Sykora et al. actually teaches away from Applicants' claimed composition for inserting a foreign molecule into a cell.

And, in addition, Applicants assert that one skilled in the art would not look to the teaching of Sykora et al. to formulate the composition of the present invention for intracellular delivery of an exogenous compound via the disclosed composition. Sykora et al. provide no teaching and no suggestion that a compound for specifically eliminating a plasmid from a dividing, gram negative, prokaryotic bacterial cell would be useful in a novel composition for inserting a plasmid, or any other compound, into a cell.

Reconsideration and allowance of Claims 18-20, 23-25, and 27 are respectfully requested.

III. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20, 23-25, and 27 under 35 U.S.C. §102(b) as anticipated by Diana et al., U.S. Pat. No. 4,022,833. According to the Examiner,

> "The '833 patent discloses at column 5, lines 25-45, N,N'-(1,6, hexylene)-bis[2-hydroxyundecylamine] with a variety of counter ions, and at Examples 91 and 92 N,N'-1,6-hexylene)-bis[[N,N'-dimethyl-2-hydroxyundecylammonium]dichloride. Thus, k=1, n=6, i.e. B=hexyl, R1, R3, R4, and R6 each are H or methyl, R2 and R5 are each undecyl, and A=chloride or phosphate." (See, Office Action, page 3.)

However, Diana et al. only teach the use of quaternary ammonium compounds for use as antibacterial agents,

> "The compounds of Formula I . . . are useful as antibacterial agents and are especially useful for disinfecting and sanitizing living and non-living surfaces by conventional swabbing, padding, spraying, immersing, rinsing and the like techniques." (See, Diana et al., column 4, lines 49-54.)

There is no disclosure in Diana et al. concerning the use of the quaternary ammonium salts disclosed therein for transfection and no disclosure or suggestion for use of the quaternary ammonium salts in a composition further comprising an exogenous compound, e.g., DNA, protein, etc., whereby the composition is capable of intracellular delivery, i.e., transfection, of the exogenous compound.

Reconsideration and allowance of Claims 18-20, 23-25, and 27 are respectfully requested.

IV. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20 and 23-27 under 35 U.S.C. §102(b) as anticipated by Quinlan, U.S. Pat. No. 3,966,630. According to the Examiner,

> "The '630 patent discloses at examples C10-C12 molecules where k=1, n=2 or 4, i.e. B=ethyl or butyl, R1, R3, R4 and R6 are methylene phosphonate, R2 and R5 are each C_{12}, C_{14}, or C_{18}, and A= bromide." (See, Office Action, page 3.)

The compounds disclosed in Quinlan are for inhibiting the buildup of "scale", i.e., alkaline earth metal cations and anions usually present in commercial-grade water. According to Quinlan,

> "I have now discovered a process for inhibiting scale such as calcium, barium and magnesium carbonate, sulfate, silicate, etc., . . . which comprises employing threshold amounts of polyquaternary ammonium methylene phosphonates." (See, Quinlan, column 2, lines 26-30.)

There is no disclosure in Quinlan concerning use of the quaternary ammonium salts disclosed therein for transfection and no disclosure or suggestion for use of the quaternary ammonium salts in a composition further comprising an exogenous compound, e.g., DNA, protein, etc., whereby the composition would be capable of intracellular delivery, i.e., transfection, of the exogenous compound.

Reconsideration and allowance of Claims 18-20 and 23-27 are respectfully requested.

V. Issue raised under 35 U.S.C. §102(b)

The Examiner has rejected Claims 18-20, 23-25, and 27 under 35 U.S.C. §102(b) as anticipated by Squibb, GB1277086. According to the Examiner,

> "The '086 document discloses at examples 1-5, hexamethylenebis-(n-decyldimethyl-ammonium)dibromide, hexamethylenebis-(n-dodecyldimethyl-ammonium)dibromide, hexamethylenebis-(n-octyldimethyl-ammonium)dibromide, hexamethylenebis-(n-nonyldimethyl-ammonium)dibromide, and hexamethylenebis-(n-undecyldimethyl-ammonium)dibromide. Thus k=1, n=6, i.e. B=hexyl, R1, R3, R4, and R6 are each methyl, R2 and R5 are each octyl, nonyl, decyl, undecyl, or dodecyl, and A=bromide." (See, Office Action, pages 3-4.)

However, Squibb discloses these compounds only for use as foliage fungicides and aquatic herbicides,

> "This invention relates to novel hexamethylenebis (alkyldimethylammonium)bromides and their use as foliage fungicides and aquatic herbicides." (See, Squibb, left column, second paragraph.)

There is no disclosure in Squibb concerning use of the quaternary ammonium salts disclosed therein for transfection and no disclosure or suggestion for use of the quaternary ammonium salts in a composition further comprising an exogenous compound, e.g., DNA, protein, etc., whereby the composition is capable of intracellular delivery, i.e., transfection, of the exogenous compound.

Reconsideration and allowance of Claims 18-20, 23-25, and 27 are respectfully requested.

VI. Nonstatutory Obviousness-Type Double Patenting

The Examiner has raised a nonstatutory obviousness-type double patenting rejection against Claims 18-26 and 28-32 as being unpatentable over Claims 1-3 and 17-28 of U.S. Pat. No. 6,733,777. The Examiner indicates that a terminal disclaimer in compliance with 37 C.F.R. §§1.321(c) or 1.321(d) may overcome this rejection.

Applicants acknowledge the double patenting rejection made by the Examiner. However, Applicants assert that the claims as amended above clearly distinguish these claims as a separate invention from the method claims of U.S. Pat. No. 6,733,777. Therefore, Applicants assert that the above-referenced claim amendments obviate the requirement for a terminal disclaimer in the present application.

Withdrawal of the double patenting rejection and allowance of Claims 1-3 and 17-28 are respectfully requested.

Entry and allowance of amended Claims 18-32 and new Claims 33-46 are respectfully requested.

Respectfully submitted,

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